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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/702,718	03/19/1997	BERND MULLER-ROBER	AGREVO-1	7038

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EXAMINER	
COLLINS, CYNTHIA E	

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 08/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/702,718	MULLER-ROBER ET AL.	
	Examiner	Art Unit	
	Cynthia Collins	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71,74-83 and 100-126* is/are pending in the application.

4a) Of the above claim(s) *78,102,103,106,107,109,110,113,114 and 126* is/are withdrawn from consideration.

5)☒ Claim(s) *77* is/are allowed.

6)☒ Claim(s) *71,74-76,79-83,100,101,104,105,108,111,112 and 115-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on July 28, 2003 and October 28, 2003 have been entered.

Claims 1-70, 72-73, 84-99 are cancelled.

Claims 121-126 are newly added.

Claims 71, 74-83 and 100-126 are pending.

Newly submitted claim 126 is directed to an invention that is independent or distinct from the originally elected invention for the following reasons: claim 26 is directed to a storage organ of a plant, which is the subject matter of nonelected Group III set forth at page 2 of the restriction requirement mailed June 7, 1999. Accordingly, claim 126 is withdrawn from consideration as being directed to a non-elected invention.

Claims 78, 102-103, 106-107, 109-110, 113-114 and 126 are withdrawn.

Claims 71, 74-77, 79-83, 100-101, 104-105, 108, 111-112 and 115-125 are examined to the extent of species VI (citrate synthase of *S. tuberosum* or SEQ ID NO:1).

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All previous objections and rejections not set forth below have been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 71, 74-76, 79-83, 100-101, 104-105, 108, 111-112 and 115-125 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims as amended are directed to a recombinant double-stranded DNA molecule comprising a promoter functional in plants and a DNA sequence encoding a citrate synthase, including a DNA sequence that has at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or encoding an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or comprising a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase, wherein said DNA sequence is fused to said promoter in antisense orientation so that the non-coding strand of said DNA sequence is transcribed and wherein said DNA sequence exhibits sufficient sequence identity to an endogenous citrate synthase gene or is of sufficient length to reduce expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule, as compared to the expression of said endogenous citrate synthase gene in a wild type plant cell, whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced

sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell or a plurality of said transgenic plant cells or a plurality of said transgenic plant cells as compared to a wild type plant. The claims are also drawn to vectors cells plants and seed comprising said DNA molecule, and a method of using said DNA molecule to inhibit flower formation.

The specification describes two recombinant double-stranded DNA molecules comprising a DNA sequence encoding a citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell. The specification describes a DNA molecule comprising a DNA sequence of the elected species of SEQ ID NO:1 encoding the complete open reading frame of a potato citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous potato citrate synthase gene in a transgenic potato plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell (pages 37-41). The specification also describes a DNA molecule comprising a DNA sequence of the nonelected species of SEQ ID NO:3 encoding the complete open reading frame of a tobacco citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous tobacco citrate synthase gene in a

transgenic tobacco plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation in a plant comprising said transgenic plant cell (pages 44-45).

The specification does not describe other recombinant double-stranded DNA molecules comprising a promoter functional in plants and other DNA sequences that encode a citrate synthase obtained from any unspecified source that have at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or that encode an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or that comprise a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase wherein said DNA sequences are fused to said promoter in antisense orientation and wherein said DNA sequences exhibit sufficient sequence identity to an unspecified endogenous citrate synthase gene or are of sufficient length to reduce expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant.

The Federal Circuit has recently clarified the application of the written description requirement. The court stated that "A description of a genus of cDNAs may be achieved by means of recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus." See *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The requirements for describing a genus of

antisense DNA sequences are analogous to the requirements for describing a genus of cDNA sequences. In the instant case Applicant has not described a representative number of species falling within the scope of the claimed genus that encompasses DNA sequences that encode a citrate synthase obtained from any unspecified source that have at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or that encode an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or that comprise a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase wherein said DNA sequence is fused to said promoter in antisense orientation and wherein said DNA sequences exhibit sufficient sequence identity to an unspecified endogenous citrate synthase gene or are of sufficient length to reduce expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant. Applicant also has not described the structural features unique to the genus that are correlated with the ability of the DNA sequences to inhibit flower formation, reduce sprouting of a tuber and/or improve storage capability of a storage organ in a plant comprising said transgenic plant cell.

Claims 71, 74-76, 79-83, 100-101, 104-105, 108, 111-112 and 115-125 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant double-stranded DNA molecule comprising a promoter functional in plants and a DNA sequence encoding a citrate synthase that has 100%

sequence identity with the nucleotide sequence of SEQ ID NO:1 or encoding an amino acid sequence that has at least 100% sequence identity with the amino acid sequence of SEQ ID NO:2 or comprising the full-length open reading frame of a DNA sequence encoding a citrate synthase, wherein said DNA sequence is fused to said promoter in antisense orientation so that the non-coding strand of said DNA sequence is transcribed and wherein said DNA sequence exhibits 100% sequence identity to an endogenous citrate synthase gene and reduces expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule, as compared to the expression of said endogenous citrate synthase gene in a wild type plant cell, and whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant, as well as for vectors cells plants and seed comprising said DNA molecule and a method of using said DNA molecule to inhibit flower formation, does not reasonably provide enablement for other DNA molecules or vectors cells plants and seed comprising other DNA molecules or methods of using other DNA molecules to inhibit flower formation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims as amended are directed to a recombinant double-stranded DNA molecule comprising a promoter functional in plants and a DNA sequence encoding a citrate synthase, including a DNA sequence that has at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or encoding an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or

comprising a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase, wherein said DNA sequence is fused to said promoter in antisense orientation so that the non-coding strand of said DNA sequence is transcribed and wherein said DNA sequence exhibits sufficient sequence identity to an endogenous citrate synthase gene or is of sufficient length to reduce expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule, as compared to the expression of said endogenous citrate synthase gene in a wild type plant cell, whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell or a plurality of said transgenic plant cells or a plurality of said transgenic plant cells as compared to a wild type plant. The claims are also drawn to vectors cells plants and seed comprising said DNA molecule, and a method of using said DNA molecule to inhibit flower formation.

The specification discloses two recombinant double-stranded DNA molecules comprising a DNA sequence encoding a citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell. The specification discloses a DNA molecule comprising a DNA sequence of the elected species of SEQ ID NO:1 encoding the complete open reading frame of a potato citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous potato

citrate synthase gene in a transgenic potato plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant comprising said transgenic plant cell (pages 37-41). The specification also discloses a DNA molecule comprising a DNA sequence of the nonelected species of SEQ ID NO:3 encoding the complete open reading frame of a tobacco citrate synthase that when fused to a promoter functional in plants in antisense orientation reduces expression of an endogenous tobacco citrate synthase gene in a transgenic tobacco plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation in a plant comprising said transgenic plant cell (pages 44-45).

The specification does not disclose other recombinant double-stranded DNA molecules comprising a promoter functional in plants and other DNA sequences that encode a citrate synthase obtained from any unspecified source that have at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or that encode an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or that comprise a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase wherein said DNA sequences are fused to said promoter in antisense orientation and wherein said DNA sequences exhibit sufficient sequence identity to an unspecified endogenous citrate synthase gene or are of sufficient length to reduce expression of said endogenous citrate synthase gene in a transgenic plant cell containing and transcribing the DNA molecule whereby said reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or

improved storage capability of a storage organ in a plant. The specification also does not disclose how to use other recombinant double-stranded DNA molecules that meet the structural limitations of the rejected claims to inhibit flower formation, reduce sprouting of a tuber and/or improve storage capability of a storage organ in a plant.

The full scope of the claimed invention is not enabled because it is unpredictable whether a DNA sequence encoding a citrate synthase that has less than 100% sequence identity with the nucleotide sequence of SEQ ID NO:1 or that encodes an amino acid sequence that has less than 100% sequence identity with the amino acid sequence of SEQ ID NO:2 or that comprises less than the full-length open reading frame of a DNA sequence encoding a citrate synthase would, when expressed from a promoter functional in plants in an antisense orientation, reduce the expression of any unspecified endogenous citrate synthase gene in a manner that would lead to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ in a plant transformed therewith.

The phenotypic effect of expressing sequences having less than 100% sequence identity with the nucleotide sequence of SEQ ID NO:1 and/or expressing sequences having less than 100% sequence identity with the endogenous target gene is unpredictable because the ability of a particular type of antisense transcript to suppress gene expression sufficiently to produce a desired phenotypic effect may depend on the degree of sequence identity between the transcript and the endogenous gene.

See, for example, Thierry et al. (Plant Molecular Biology, 1996, Vol. 32, pages 1075-1083), who teach that a bean transgene comprising a Nii1 gene that has 76% identity with the leaf-specific tobacco Nii1 gene escapes silencing by the tobacco

transgenic 271 locus that comprises the leaf-specific tobacco Nii1 gene in an antisense orientation under the control of the CaMV promoter, whereas the native tobacco root-specific Nii1 gene that has 84% identity with the leaf-specific tobacco Nii1 gene does not escape such silencing (page 1075 abstract; page 1077 Figure 1; page 1078 Table 1; page 1079 Figure 2; page 1080 Table 2; page 1081 Figure 3).

The phenotypic effect of expressing sequences that comprise less than the full-length open reading frame of a DNA sequence encoding a citrate synthase is unpredictable because the ability of a particular type of antisense transcript to suppress gene expression sufficiently to produce a desired phenotypic effect may depend on the length of the transcript and its position relative to the endogenous gene.

See, for example, Sandler et al. (Plant Molecular Biology, 1988, Vol. 11, No. 3, pages 301-310) who teach that when expressed as antisense transcripts, DNA fragments encoding different portions of the nopaline synthase gene vary in their ability to inhibit nopaline synthase gene expression (page 308 column 2 and Table 4, page 309 column 1 first full paragraph). Antisense transcripts downstream from the Cla I site (nucleotide 373) effectively suppressed nopaline synthase gene expression, whereas the full length antisense transcript and the antisense transcript upstream from the Cla I site (nucleotides 1 to 373) did not (id).

See also, for example, van der Krol et al., who teach a method of decreasing the expression of an endogenous petunia chalcone synthase gene by transforming petunia cells with chimeric genes comprising chalcone synthase (CHS) coding sequences operably linked in an antisense orientation to a CaMV 35S constitutive promoter (Plant Molecular Biology, 1990, Vol. 14, pages 457-466). The full length CHS cDNA and CHS

sequences encoding half-length or quarter-length RNA complementary to the 3' half of the CHS mRNA decreased the expression of endogenous CHS, whereas half-length RNA complementary to the 5' half of the CHS mRNA did not (page 460 Figures 1 and 2; page 461 Figure 3).

The phenotypic effect of expressing sequences that comprise less than the full-length open reading frame of a DNA sequence encoding a citrate synthase is additionally unpredictable because the effect of antisense expression on phenotype may vary depending on the level of suppression of endogenous gene expression, which level of suppression could be affected by the degree of sequence identity between the transcript and the endogenous gene and the length of the transcript and its position relative to the endogenous gene.

See, for example, Golovkin et al. (Plant Physiology, 2003, Vol. 132, pages 1884-1891), who teach that transgenic *Arabidopsis* plants in which the level of U1 snRNP gene expression was more highly suppressed (having higher levels of antisense transcript and lower levels of endogenous gene expression) were phenotypically different (severe flower phenotype with only sepals and carpels in mature flowers) from transgenic *Arabidopsis* plants in which the level of U1 snRNP gene expression was less suppressed (having visibly normal flowers or abnormal flowers with rudimentary or partially developed petals and stamens, and having lower levels of antisense transcript and higher levels of endogenous gene expression). Paragraph spanning pages 1885-1886; page 1886 Figure 2; page 1887 Figure 3; page 1887 Figure 4B; page 1888 paragraph spanning columns 1 and 2 and Figure 5B).

Absent guidance with respect to how to use antisense sequences that have at least 80% sequence identity with the nucleotide sequence of SEQ ID NO:1 or that encode an amino acid sequence that has at least 80% sequence identity with the amino acid sequence of SEQ ID NO:2 or that comprise a portion of at least 15 base pairs of a DNA sequence encoding a citrate synthase to reduce expression of an unspecified endogenous citrate synthase gene in a transgenic plant cell whereby the reduced citrate synthase expression leads to inhibition of flower formation, reduced sprouting of a tuber and/or improved storage capability of a storage organ, it would require undue experimentation for one skilled in the art to make and use the claimed DNA constructs, as one skilled in the art would have to resort to trial and error experimentation by testing each DNA sequence that meets the structural limitations set forth in the claims for its effect on flower formation, tuber sprouting and/or storage organ storage capability, in order to discriminate between those DNA sequences that have the desired functional characteristics and those that do not.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 111, 119 and 120 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 111, 119 and 120 are drawn to seeds, but are not limited to seeds that comprise the construct that was introduced into the parent plant. Due to Mendelian

inheritance of genes, a single gene introduced into the parent plant would only be transferred to half of the seeds of that plant. In addition, given that there is no indication that there would be any other distinguishable characteristics of the claimed seeds, it is unclear whether the claimed seeds would be distinguishable from seeds that would occur in nature. See *Diamond v. Chakrabarty,* 447 U.S. 303 (1980), *Funk Bros. Seed Co. V. Kalo Inoculant Co.*, 233 U.S. 127 (1948), and *In re Bergey*, 195 USPQ 344, (CCPA). The amendment of the claims to recite that the seeds comprise in their genome the recombinant double stranded DNA molecule that was introduced into the parent plant would overcome the rejection.

Remarks

Claim 77 is allowed.

Claims 71, 74-76, 79-83, 100-101, 104-105, 108, 111-112 and 115-125 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia Collins whose telephone number is (571) 272-0794. The examiner can normally be reached on Monday-Friday 8:45 AM -5:15 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Cynthia Collins Cynthia Collins 8/7/04